UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/721,763	11/26/2003	Eiji Mori	081356-0207	6356

22428 7590 01/09/2007
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,763	MORI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006 and 25 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-104 and 108-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-104 and 108-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/04,7/21/04,3/28/05,11/3/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I and species (b)(antibody which binds to TRAIL-R2) in the reply filed on 7/14/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

The substitute specification filed 6/7/04 has been entered.

The disclosure is objected to because of the following informalities: There are a number of instances where multiple words are not separated, such as p. 118, first line of first full paragraph, "ofmonomer", and p. 120, 8 lines from the bottom, "antibodyhad". The whole specification should be carefully reviewed for similar instances.

Appropriate correction is required.

The abstract of the disclosure is objected to because of the following informalities: in section (c) it says "having activity to induce apoptosis". This is not proper grammar and should be either " having the activity of inducing apoptosis" or "having the ability to induce apoptosis"; also "an anti-...antibodies" is incorrect grammar.

Correction is required. See MPEP § 608.01(b).

The amendment filed 6/7/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Examples 17-31, everything relating to Figures 12-20, every reference to monomer and exogenous factors.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claims 64, 69, 109 and 110 are objected to because of the following informalities: carcinomacell(s) should be two words (see two occurrences in "survival" paragraph of step (4). Appropriate correction is required.

Claims 100 and 101 recite "constant region of the said antibody which is bound to TRAIL-R", which excludes the function fragment of the antibody that binds TRAIL-R. It does not appear this was applicants' intent. Adding in the last line "or a functional fragment thereof" after "said antibody" would clarify this.

Claims 64, 69, 74, 79 and 109-112 are not completely clear since they recite "the following test" and list a number of different things, each of which could be viewed as an individual test. This claim could be clarified by adding before (1), "said test comprising the following steps:"

Claim 84 ends with a comma.

Claim 108 in (v) and (vi) says "the activity to induce apoptosis". This is not proper grammar and should be either " the activity of inducing apoptosis" or " the ability to induce apoptosis".

Claims such as 63, 64, 69, 74, 79 and 109-112 which recite "has the same subclass with the antibody..." is incorrect grammar. This phrase could be reworded as "is the same subclass as".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100, 104, 108-112 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63, 64, 69, 74, 79, 84, 89, 94 and 100 are indefinite because it is unclear if the phrase "monomer independently of exogenous factors" is modifying the antibody or TRAIL-R.

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100 and 108 are indefinite for reciting "as a monomer". This rejection assumes the term "monomer" in the claims is modifying the antibody

and not the receptor because there is no discussion of a monomer receptor, though they exist. While the specification says (two paragraphs beginning with the second to last line of page 20) that a monomer antibody means an antibody present in a fraction in which a monomer is clearly eluted when antibodies are separated and purified, it is unclear if, for example, a monomer is distinct from a monoclonal antibody or simple means that the antibodies are not multimerized so a monomer could include distinct antibodies (*e.g.*, polyclonal antibodies but not IgM antibodies) of the same weight which do not multimerize. It is unclear if a monomer antibody is an "active" antibody as the term is used by the specification so that, for example, disclosed antibody 0304 is a monomer antibody and H-48-2 is not. The term "monomer" needs to be clarified in the claims.

Claims 63, 64, 69, 74, 79, 84, 89, 94 and 100 are indefinite for reciting "exogenous factor". The specification in the last paragraph of p. 21 defines an exogenous factor as a factor other than an antibody. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The meaning in the specification is repugnant to the art. As defined in Stedman's Medical Dictionary, 27th Ed., exogenous means "Originating or produced outside of the organism. SYN: ectogenous, exogenetic. [exo- + G. *-gen,* 1 production]."

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100 and 108 are indefinite because of the use of the term "TRAIL-R". Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "TRAIL-R" in the claims is *apparently* used by the claims to mean "TRAIL receptors", while the accepted meaning is "TRAIL-R2" or "DR5." The term is indefinite because the specification does not clearly redefine the term. It appears the term "TRAIL-R" in claims is used by the claims to mean "TRAIL receptors", but the claims seem to use it in the singular. The specification discusses TRAIL-R1 and TRAIL-R2 as being TRAIL receptors." The term is indefinite because the specification does not clearly redefine the term. US 6,072,047 (D4, cited by Applicants in the IDS filed 11/30/05) defines TRAIL-R as a specific TRAIL receptor (SEQ ID NO:2 of the

patent). Other terms for TRAIL-R are DR5 and TRAIL-R2. However, the instant claims already use the term TRAIL-R2 and it would be inconsistent to use two different terms for the same receptor in an application and its claims. Because the claims of the instant application say "carcinoma cells expressing TRAIL-R", it appears that a single receptor is being referred to. If applicants intend that the carcinoma cells are expressing TRAIL receptors, then the claim should reflect this. If it is intended that the cells are expressing TRAIL-R2, then the claims should state this clearly.

Claims 63, 64, 69, 74, 79 and 109-112 are indefinite because it is not known what "reducibility of the mitochondria" means. This phrase is not defined in the specification or well known in the art.

Claims 89, 94, 100 and 101 recite the limitation "the [or said] antibody bound to TRAIL-R" in the last or second to last line of claims 100-101 and in the 4-5 lines from end of claims 89 and 94. There is insufficient antecedent basis for this limitation in the claim. There is only antecedent basis for 'the antibody bound to TRAIL-R2'.

Claims 84, 89, 94 are indefinite because it is not clear in the last line if the 80% or less refers to the antibody of (4) or the survival. This rejection could be obviated by moving the 80% to immediately follow "survival rate of", if appropriate.

Claims 64, 69, 74, 79, 109-112 are indefinite because they recite in step (4): "wherein "a" represents the measured value of a well tested". All the wells are being tested. It is unclear if this reference is to the well with the TRAIL-R2 antibody.

Claims 64, 69, 74, 79 and 109-112 are additionally indefinite because they recite in step (4): "wherein "a" represents the measured value of a well tested", and it is not clear what value is being measured. If it is the percent survival, for example, that needs to be stated.

Claim 108 recites the limitation "the antigenicity" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Regarding claim 104, the phrase "or the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 63-107 were added 6/7/04 when the substitute specification was submitted. As originally filed, there is insufficient support in the specification for the limitations in these claims (see the above objection to the specification for containing new matter).

Priority

While certified copies of all priority documents have been received, none are translated.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 120 or 119(a)-(d), a certified English translation of the Japanese applications must be submitted. The filing date of the priority document is not perfected unless applicant has filed a certified priority document in the application (and an English language translation, if the document is not in English) (see 37 CFR 1.55(a)(3)) and the examiner has established that the priority document satisfies the enablement and description requirements of 35 U.S.C. 112, first paragraph (see MPEP 706.02(b)).

Because the instant application is a CIP of PCT/JP02/04816, it is critical that the PCT be translated for priority determination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 63-104 and 108 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et al. (J. Immunol., 162:2597, 1999; A16, IDS filed by Applicants 6/7/04).

Griffith et al. teach monoclonal antibody M413 to DR5 (a.k.a. TRAIL-R2) that induces apoptosis in cells, including human melanoma cancer cells (Figs. 2-3). Further, Figure 2 shows that at least for WM 9 cells, soluble M413, which is not crosslinked (*i.e.*, which induces apoptosis in carcinoma cells expression a TRAIL receptor independent of exogenous factors), induces cell death in human melanoma cells at a concentration less than 1 μg/ml. Also, soluble M413 was able to inhibit TRAIL-induced cell death (Fig. 5). The antibody of Griffith et al. was purified by protein A affinity chromatography (p. 2598, end of first paragraph). It was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see first paragraph of p. 2598).

Griffith et al. are silent with respect to the % cell survival at the concentration specified in the instant claims in Colo205 cells, but it appears absent evidence to the contrary that antibody M413 has the required functional properties required by the instant claims.

Claims 63-104 and 108 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,342,369.

US 6,342,369 teaches antibody 16E2, which has *in vitro* cell death-inducing activity in the absence of crosslinking at concentrations less than 1 μg/ml as shown in Figure 13C, where it had agonistic, *i.e.*, apoptotic, activity at a concentration of 0.4 μg/ml for SK-MES-1 (human lung carcinoma cell line cells, col. 53, lines 8-9) when not crosslinked. The antibody was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see Example 9).

US 6,342,369 did not use the same assay used to characterize the claimed antibody in the instant claims, but it appears absent evidence to the contrary that antibody 16E2 has the required functional properties required by the instant claims.

Claims 63-104 and 108 are rejected under 35 U.S.C. 102(e) or 102(a) as being anticipated by US 2003/0190687.

US 2003/0190687 teaches TRA-8 antibody to TRAIL-R2. The antibody induces apoptosis in carcinoma cells (see, for example, Example 8 and Figures 2c, 3b). The antibody was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see Examples 2 and 3). TRA-8 appears to have all the properties, absent evidence to the contrary, of the instantly claimed antibodies.

The PTO does not have facilities for examining and comparing Applicants' claimed antibody with the prior art, and thus Applicants have the burden of persuasion to make some comparison between materials in order to establish unexpected properties for the claimed. Applicants can be required to prove that prior art products do not necessarily or inherently possess characteristics of the claimed antibodies. *Ex parte Gray*, 10 USPQ2d 1922 (BPAI 1989) and *In re Best,* 195 USPQ 430, 433 (CCPA 1977).

Alternative Names

TRAIL-R2 is also known as TRAIL 2, TR7, Trick2, Apo-2, DR5, Tango63e, TNFRSF10B and Killer

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

December 14, 2006